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Research Highlight

Do Substantia Nigra Dopaminergic Neurons Differentiate Between Reward and Punishment?

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The activity of dopaminergic neurons are thought to be increased by stimuli that predict reward and decreased by stimuli that predict aversive outcomes. Recent work by Matsumoto and Hikosaka challenges this model by asserting that stimuli associated with either rewarding or aversive outcomes increase the activity of dopaminergic neurons in the substantia nigra pars compacta.

A wealth of evidence over the past two decades has implicated the dopaminergic system in encoding 'reward prediction errors' (RPEs). That is, when animals and humans experience a reward or an event that is better than expected, midbrain dopaminergic neurons exhibit phasic burst firing, with the magnitude of the firing-rate increase correlated with the degree to which the outcome is better than expected. Conversely, events that are worse than expected are accompanied by pauses of dopaminergic firing, with the duration of pause correlating with the degree to which events are worse than expected. These findings, originally reported by Schultz and colleagues (1997) have now been demonstrated across multiple labs and species, including monkeys, rats and humans. This biphasic modulation of dopamine cell activity is thought to act as a 'teaching signal' by modifying synaptic connections in the striatum to promote the selection of actions that produce positive outcomes and to diminish the selection of those that do not (Wickens et al., 2003; Cohen and Frank, 2009). Indeed, recent optogenetic studies have confirmed that phasic, but not tonic, stimulation of dopaminergic cells induces behavioral conditioning: animals spend more time in locations in which they had received such stimulation compared with those in which they had not (Tsai et al., 2009).

It is widely assumed that all midbrain dopaminergic cells, from the ventral tegmental area (VTA) to the substantia nigra pars compacta (SNc), convey a common, global RPE signal. In a recent *Nature* article, Matsumoto and Hikosaka (2009) have challenged this assumption. They trained monkeys with a classical conditioning procedure in which some stimuli were strongly or weakly predictive of a liquid reward, whereas other stimuli were strongly predictive of an aversive airpuff to the face. They found that one class of neurons, located more ventromedially in the region of the VTA, responded just as predicted by the RPE hypothesis: phasic firing increases were elicited by the reward-predictive stimuli, and phasic depressions were elicited by the airpuff-predictive stimuli. When the outcomes themselves were experienced, phasic spiking was only observed when the outcome was more rewarding or less aversive than expected, whereas transient pauses were seen only when expected rewards were withheld.

However, in contrast to the current model, Matsumoto and Hikosaka (2009) identified presumptive dopaminergic neurons in the SNc region that were phasically activated by conditioned stimuli associated with both rewarding and aversive outcomes. This unidirectionality was also observed during the outcome itself, particularly if its presentation was unexpected. Thus, these cells appear to encode something akin to salience, perhaps reflecting the absolute value of RPE.

One limitation of the Matsumoto and Hikosaka study is that the neurons recorded were not histochemically identified. As in most *in vivo* studies, neurons were identified using electrophysiological criteria and their phasic excitation to free reward. Although this strategy has been used widely, there are reasons to question whether it is water-tight. For example, Ungless et al. (2004) found mesencephalic neurons excited by aversive stimuli that were non-dopaminergic interneurons, in spite of having electrophysiological features like dopaminergic neurons. The problem with this interpretation is that Matsumoto and Hikosaka did not find a population of neurons with a 'normal' (RPE) pattern of response intermingled with this novel group of neurons in the SNc, as would be expected from sampling of dopaminergic and non-dopaminergic neurons. A more recent study in rats by Brishcoux et al. (2009) using a combination of identification strategies, has corroborated the Matsumoto and Hikosaka finding that there are mesencephalic dopaminergic neurons activated by aversive stimuli, but they are rare, possibly because of the use of anesthetic. Another issue is location. Brischoux et al. provided strong evidence that there are neurons

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(even if rare) excited by aversive stimuli within the VTA, whereas Matsumoto and Hikosaka contend based upon less precise recording depth measurements that these neurons are largely within the SNc. This could be a species-related difference.

If true, this finding necessitates a paradigm shift in thinking how experience engages dopaminergic neurons to reshape neural circuitry. In the striatal regions regulated by the VTA (ventromedial striatum), phasic dopamine release in response to positive RPE should preferentially activate low affinity D_1 dopamine receptors, promoting the response of striatonigral medium spiny neurons to sensorimotor-linked cortical activity, both by increasing synaptic strength and postsynaptic excitability; this should promote selection of actions associated with reward. Conversely, transient drops in dopamine release in response to negative RPE should deactivate tonically active, high affinity D_2 receptors, promoting the activity of striatopallidal mediums spiny neurons, both by increasing synaptic strength and postsynaptic excitability; this should promote the suppression of actions associated with aversive outcomes (Shen et al., 2008; Cohen and Frank, 2009). In the striatal regions regulated by the SNc (dorsolateral striatum), the response to positive RPEs should be the same. But the results of Matsumoto and Hikosaka predict that stimuli with a negative RPE should evoke the same alterations in striatal circuitry—leading to action selection rather than action suppression.

A possible resolution to this conundrum may lie in the uncertainty about whether the conditioned stimulus associated with the aversive airpuff in the Matsumoto and Hikosaka study had positive or negative motivational valence. The most straightforward inference about the airpuff-associated conditioned stimulus is that it had a negative RPE. But it is possible that it had a positive RPE in this paradigm because the conditioned stimulus allowed the monkey to blink and reduce the unpleasantness of the airpuff. This interpretation helps explain the partial dissociation between the responses of dopaminergic neurons to the conditioned and unconditioned aversive stimuli: there was a much smaller percentage (11%) of neurons excited by unconditioned aversive stimuli than by conditioned aversive stimuli (37%) (and a far greater proportion—47%—were inhibited by the unconditioned aversive stimuli). Moreover, avoidance of an expected negative outcome, or termination of an experienced one, is associated with increases in dopamine and activates brain areas associated with reward (Kim et al., 2006; Brischoux et al., 2009). Furthermore, stimuli that are predictive of this release from aversion may acquire some positive motivational values in that they represent 'safety signals'—i.e. the knowledge that an aversive outcome can be avoided. Accordingly, the ability to avoid aversive outcomes is dopamine-dependent (Beninger et al., 1980; Moutoussis et al., 2008). One problem with this explanation is it is not clear why these stimuli should be interpreted differently by SNc and VTA neurons. It is possible that the VTA neurons are primarily concerned with Pavlovian states (the CS state signals that there is potential for an upcoming aversive outcome) which are encoded in ventral striatum, whereas SNc neurons participate in reinforcing instrumental actions (e.g. blinking) encoded in dorsolateral striatum that would act to improve the predicted state (O'Doherty et al., 2004).

The alternative explanations aside, the study by Matsumoto and Hikosaka clearly challenges our ideas about how dopamine signaling is regulating the striatonigral and striatopallidal circuitry in the dorsolateral striatum and suggests that there may be other factors in play that we do not understand. What those other factors might be—thalamostriatal signals, interneurons—remains to be defined, but the intriguing work by Matsumoto and Hikosaka forces us to ask the question.

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